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# Interleukin 4 Inhibits Stimulation of Hepatic Lipogenesis by Tumor Necrosis Factor, Interleukin 1, and Interleukin 6 but not by Interferon-$\alpha$[1]

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## ABSTRACT

**Multiple cytokines stimulate hepatic lipogenesis in rodents. We have previously shown that lipogenic cytokines can be divided into 2 classes by their mechanism of action and their synergistic interactions. We now report the effects of interleukin 4, a cytokine known to inhibit the synthesis and action of other cytokines. Interleukin 4 by itself did not alter hepatic lipogenesis. However, interleukin 4 inhibited the characteristic stimulation of hepatic lipogenesis that is seen with tumor necrosis factor, interleukin 1, and interleukin 6. These 3 cytokines stimulate hepatic lipogenesis by the same mechanism, increasing hepatic levels of citrate, a key allosteric activator of acetyl CoA carboxylase, the rate-limiting enzyme of fatty acid synthesis. Interleukin 4 blocks the ability of tumor necrosis factor to increase hepatic citrate. In contrast, interleukin 4 does not block the stimulation of hepatic lipogenesis by interferon-$\alpha$, a cytokine that increases hepatic lipogenesis by a mechanism other than increasing hepatic citrate levels. These results demonstrate that interleukin 4 can inhibit the metabolic action of selected cytokines, which provides strong support for our proposal that lipogenic cytokines operate through 2 distinct mechanisms of action and can therefore be divided into 2 separate classes based on their interactions. These results also emphasize the multiple relationships between the immune response and lipid metabolism.**

## INTRODUCTION

The host response to infection and cancer includes marked disturbances in intermediary metabolism, such as hypertriglyceridemia due to increases in serum VLDL[3] (1–4). These metabolic disturbances are thought to be mediated by the cytokines responsible for coordinating the immune response (5–8). Early studies focused on the effects of cytokines on cultured fat cells. TNF, IL-1, and the interferons decrease the synthesis of LPL in cultured 3T3-L1 adipose cells (5–7). Decreases in LPL could increase serum triglycerides by decreasing clearance of triglyceride-rich lipoproteins.

However, recent data indicate that TNF increases serum triglyceride levels *in vivo* by stimulating hepatic lipogenesis and VLDL production, not by inhibiting adipose tissue LPL activity and triglyceride clearance (reviewed in Ref. 7). TNF administration to rats produces very little change in LPL activity in adipose and muscle tissue, and TNF has no effect on triglyceride clearance under conditions in which TNF produces rapid and sustained increases in serum triglycerides (9–12). On the other hand, TNF induces an increase in hepatic lipogenesis and VLDL production that is rapid enough to account for the rise in serum triglycerides (11–14).

Therefore, our laboratory has focused on the regulation of hepatic lipogenesis by cytokines. Using mice, we have demonstrated that in addition to TNF, IL-1 and IFN-$\alpha$ stimulate hepatic lipogenesis (15). The effects of these 3 cytokines are rapid, occurring within 30 min and peaking within 2 h, but extend for up to 17 h after a single administration. The concentrations required for TNF and IL-1 to stimulate hepatic lipogenesis are similar to those required to induce fever (15–17). The dose of IFN-$\alpha$ is similar to that which inhibits murine tumor cell growth *in vivo* (15, 18). IL-6, a potential mediator of the actions of TNF and IL-1 (19–24), also stimulates hepatic lipogenesis, but with a shorter time course (25).

Studies on the mechanism by which these cytokines stimulate hepatic fatty acid synthesis and the interactions between these cytokines led us to propose that there are 2 classes of cytokines that stimulate hepatic lipogenesis (26). TNF, IL-1, and IL-6 increase hepatic fatty acid synthesis by increasing hepatic levels of citrate, an allosteric activator of acetyl CoA carboxylase (the rate-limiting enzyme for fatty acid synthesis); in contrast, IFN-$\alpha$ has no effect on hepatic citrate levels (25–27). When a low dose of IFN-$\alpha$ is combined with a low dose of either TNF or IL-1, striking synergy is seen in the ability of the combination to stimulate hepatic lipogenesis; in contrast, there is no synergy between low doses of TNF and IL-1 (26). When a high dose of IFN-$\alpha$ is combined with maximal doses of TNF or IL-1, an additive effect is seen on hepatic lipogenesis; in contrast, maximal doses of TNF and IL-1 are not additive (26). Thus, we have tentatively divided cytokines into 2 classes; class 1 cytokines (TNF, IL-1, and IL-6) increase hepatic fatty acid synthesis by increasing hepatic citrate levels, whereas class 2 cytokines (IFN-$\alpha$) increase hepatic fatty acid synthesis by an as yet unknown mechanism (25, 26).

IL-4 (also called BSF-1) was first described as a costimulant for the proliferation of B-cells (28). Under appropriate conditions, IL-4 can also stimulate the growth of T-cells and act as a costimulant for mast cells (reviewed in Refs 29 and 30). In addition, IL-4 influences function of B-lymphocytes and multiple other hematopoietic cells. IL-4 can inhibit production of TNF, IL-1, and prostaglandin $E_2$ by activated macrophages (31, 32). Recent data indicate that IL-4 can block certain actions of some cytokines. IL-4 prevents activation of natural killer cells and proliferation of B-cells induced by IL-2 (33–37). In addition, IL-4 decreases TNF-induced synthesis of complement factor B in fibroblasts (38).

In this paper, we demonstrate that IL-4 can block a metabolic effect of TNF, IL-1, and IL-6—the ability to stimulate hepatic lipogenesis. However, IL-4 has no effect on the ability of IFN-$\alpha$ to stimulate hepatic lipogenesis. These data support our conclusion that lipogenic cytokines have 2 distinct mechanisms of action in stimulating hepatic lipogenesis and can therefore be divided into 2 classes.

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[3] The abbreviations used are: VLDL, very low-density lipoprotein; TNF, tumor necrosis factor; IL, interleukin; IFN, interferon; LPL, lipoprotein lipase.

## MATERIALS AND METHODS

**Materials.** $^3H_2O$ (1 Ci/g) was purchased from ICN Radiochemicals, Irvine, CA, $^{14}C$-labeled oleic acid (40–60 mCi/mmol) was from New England Nuclear, Boston, MA, and Ready Safe Scintillation fluid was from Beckman, Fullerton, CA. Human TNF-$\alpha$ with a specific activity of $5 \times 10^7$ units/mg was provided by Genentech, Inc., South San Francisco, CA. Recombinant human IL-1$\beta$ (AA112-269) with a specific activity of $5 \times 10^7$ units/mg was produced as described previously (16). Recombinant human IFN-$\alpha$ A/D with a specific activity of $7.9 \times 10^7$ units/mg was provided by Drs. M. Brunda and P. Sorter of Hoffman-LaRoche Inc., Nutley, NJ. IL-6 (39), with a specific activity of $1.7 \times 10^8$ units/mg, was purified from the media of transformed yeast cells.[4] Recombinant murine IL-4, with a specific activity of $>10^8$ units/mg protein in the standard anti-immunoglobulin co-mitogenesis genesis assay (40), was provided by Dr. S. Gillis of Immunex, Seattle, WA.

**Animals.** Male mice (C57BL/6J) were purchased from Bantim Kingman, Freemont, CA. Animals were fed Purina Mouse Chow and water *ad libitum*. On the morning of the study, groups of animals were given i.m. injections of cytokine or normal saline as controls. TNF and IL-6 were administered in 0.9% saline, whereas IL-1, IL-4, and IFN-$\alpha$ were in a 0.9% saline/0.1% serum human albumin solution. There was no effect of 0.1% human serum albumin on hepatic lipogenesis in previous experiments (15).

Studies using multiple cytokines presented here and previously (15, 25, 26) have been performed with mice because this allows for the use of small quantities of cytokines. Human IFN-$\alpha$ A/D has been shown to be active in mouse tissues in a manner similar to that of mouse IFN-$\alpha$ (41, 42).

**Measurement of Lipogenesis.** Hepatic lipogenesis was measured using a technique that has been previously described in detail (15, 43, 44). In brief, mice were given i.p. injections of tritiated water (20 mCi) at the time after cytokine administration indicated in the text. One h later, the animals were anesthetized, blood was obtained, and livers were removed and weighed. Hepatic lipids were then saponified in a KOH/ethyl alcohol solution (15, 43, 44). After addition of labeled internal standards, cholesterol was extracted with petroleum ether. The remaining mixture was acidified followed by extraction of fatty acids. Synthesis of lipid was assessed by liquid scintillation counting (15, 43, 44).

**Hepatic Citrate Levels.** Citrate levels were measured *in situ* as described previously (27). In brief, a lobe of liver was frozen *in situ* using a Wollenberger clamp cooled in liquid $N_2$. Citrate was then extracted in 8% $HClO_4$ in 40% ethyl alcohol. After centrifugation, the supernatant was neutralized. Citrate was measured by an enzymatic assay (27).

**Statistics.** Data are presented as mean ± SEM. Significance for multiple comparisons was calculated using analysis of variance.

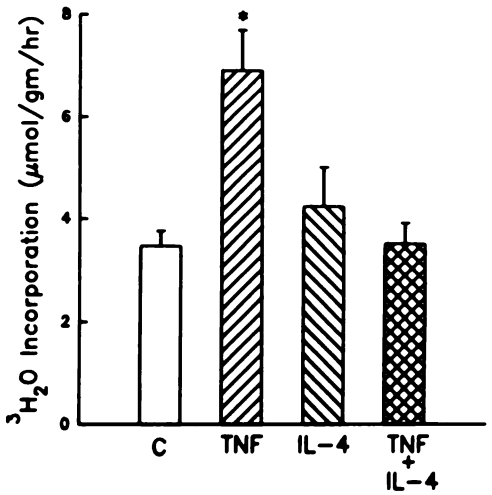


Fig. 1. IL-4 suppresses TNF-stimulated hepatic lipogenesis. Animals were given injections of saline, TNF (500 ng), IL-4 (100 ng), or a combination of TNF (500 ng) and IL-4 (100 ng). Sixty min later, animals were given injections of 20 mCi $^3H_2O$. After an additional 60 min, hepatic lipogenesis was measured by incorporation of $^3H_2O$ into fatty acid as described in "Materials and Methods." Values are mean ± SE (*bars*). $n = 10$ for all groups. * $P < 0.002$ compared with control or TNF + IL-4, $P < 0.01$ compared with IL-4.

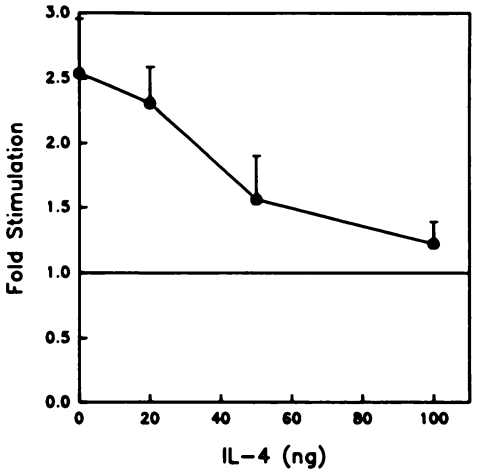


Fig. 2. Dose-response curve for IL-4 suppression of TNF-stimulated hepatic lipogenesis. Control animals were given injections of saline, whereas experimental animals were given injections of 500 ng TNF plus the amount of IL-4 indicated (*abscissa*). Hepatic lipogenesis was measured by incorporation of $^3H_2O$ into fatty acids, as described in Fig. 1 and "Materials and Methods." Data are expressed as -fold stimulation over control. Values are mean ± SE (*bars*) of 4 experiments.

## RESULTS

**Effect of IL-4 on TNF-stimulated Hepatic Lipogenesis.** As seen previously, TNF (500 ng/20 g mouse) stimulates hepatic lipogenesis by approximately 2-fold between 1 and 2 h after administration (Fig. 1). In contrast, IL-4 (100 ng) has no effect on hepatic lipogenesis (Fig. 1). Doses of IL-4 as high as 1 $\mu$g have no effect on hepatic lipogenesis when measured 1–2 h after administration. However, simultaneous administration of IL-4 (100 ng) prevents the ability of TNF (500 ng) to stimulate hepatic lipogenesis (Fig. 1).

The dose-response curve for IL-4 inhibition is presented in Fig. 2. A dose-dependent inhibition of TNF action is seen, with an $ED_{50}$ value of 42 ng/mouse. Maximal inhibition was produced with 100 ng of IL-4 per mouse. In multiple experiments, at maximal suppression, IL-4 decreased TNF-stimulated hepatic lipogenesis by 86 ± 11%.

**Mechanism by Which IL-4 Inhibits TNF-stimulated Lipogenesis.** We have previously shown that TNF stimulates hepatic lipogenesis by increasing hepatic levels of citrate, the key allosteric activator acetyl CoA carboxylase, the rate-limiting enzyme for fatty acid synthesis (12, 27). In the experiment shown in Fig. 3, administration of TNF again led to increases in hepatic citrate levels. In contrast, IL-4 had no effect on hepatic citrate. However, the simultaneous administration of IL-4 with TNF blocked the ability of TNF to increase hepatic citrate levels (Fig. 3).

**Effect of IL-4 on IL-1- and IL-6-stimulated Hepatic Lipogenesis.** IL-1 is another monokine that stimulates hepatic lipogenesis by a mechanism similar to that of TNF (15, 26). As seen previously, IL-1 also stimulated hepatic lipogenesis 2-fold (Fig. 4). Administration of IL-4 prevented stimulation of hepatic lipogenesis by IL-1 (Fig. 4).

IL-6 is a potential mediator of TNF and IL-1 action (19–24).

[4] Y. Guisez *et al.*, manuscript in preparation.

Hepatic lipogenesis was increased only during the first hour after IL-6 administration (25) (Fig. 5). When IL-4 was administered before IL-6, IL-4 blocked the ability of IL-6 to stimulate hepatic lipogenesis (Fig. 5).

**Effect of IL-4 on IFN-α-stimulated Hepatic Lipogenesis.** As seen previously, IFN-α stimulated hepatic lipogenesis by 2.5-fold (Fig. 6). However, when IL-4 was administered simultaneously with IFN-α, in a protocol identical to that which inhibited TNF and IL-1, IL-4 was unable to block the ability of IFN-α to stimulate hepatic lipogenesis (Fig. 6).

## DISCUSSION

The ability to stimulate hepatic lipogenesis is shared by multiple cytokines that are involved in the immune and inflammatory responses (6, 7, 15, 25). We have previously proposed that cytokines can be divided into 2 classes by their mechanisms of action and by their synergistic interactions (26). Class 1 cytokines include TNF, IL-1, and IL-6, which increase hepatic lipogenesis by increasing hepatic levels of citrate, an allosteric activator of acetyl CoA carboxylase, the rate-limiting enzyme of fatty acid synthesis. Class 2 cytokines include at this time only IFN-α, whose mechanism of action is as yet unknown. There is synergy or additivity when class 1 and class 2 cytokines are combined. However, there is no synergy or additivity between class 1 cytokines (26).

The data presented here indicate that IL-4 is another cytokine that is capable of modulating hepatic lipogenesis. However, IL-4 has no intrinsic activity at stimulating (or inhibiting) hepatic lipogenesis under basal conditions. Rather, administration of IL-4 prevented class 1 cytokines (TNF, IL-1, or IL-6) from stimulating hepatic lipogenesis. In contrast, IL-4 had no effect on the ability of IFN-α, a class 2 cytokine, to stimulate hepatic lipogenesis. The ability of IL-4 to inhibit cytokine expression

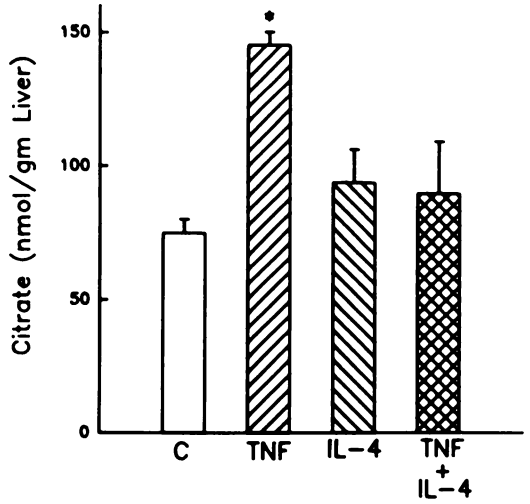


Fig. 3. IL-4 suppression of TNF induced increases in hepatic citrate levels. Animals were given injections of saline, TNF (500 ng), IL-4 (100 ng), or a combination of TNF (500 ng) and IL-4 (100 ng). Ninety min later, livers were frozen *in situ* and extracted for measurement of citrate as described in "Materials and Methods." $n = 5$ for each group. Values are mean ± SE (*bars*). * $P < 0.02$ compared with control.

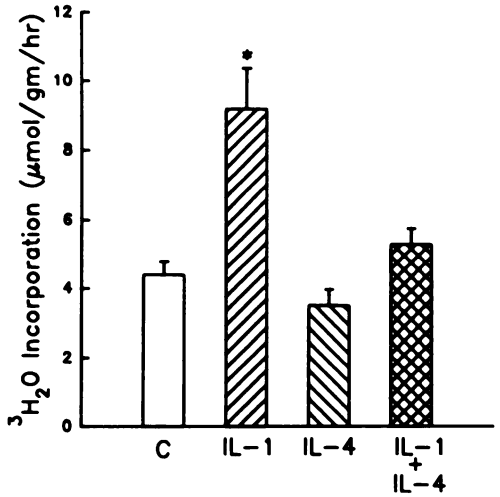


Fig. 4. IL-4 suppresses IL-1-stimulated hepatic lipogenesis. Animals were given injections of saline for controls, IL-1 (40 ng), IL-4 (100 ng), or the combination of IL-1 (40 ng) and IL-4 (100 ng), and hepatic lipogenesis was measured as in Fig. 1. $n = 10$ for all groups except for control, where $n = 9$. Values are mean ± SE (*bars*). * $P < 0.001$ compared with all of the groups.

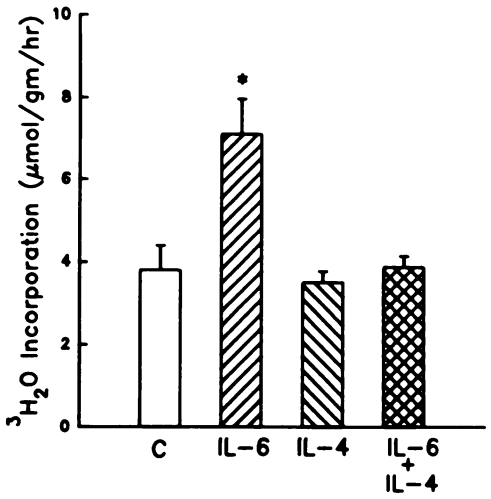


Fig. 5. IL-4 suppresses IL-6-stimulated hepatic lipogenesis. Animals were given injections of IL-4 (100 ng) or saline as indicated. Thirty min later, animals were given injections of IL-6 (1 μg) or saline as indicated followed immediately by 20 mCi of $^3H_2O$. After an additional 60 min, hepatic lipogenesis was measured as described in "Materials and Methods." $n = 5$ for each group. * $P < 0.05$ compared with control.

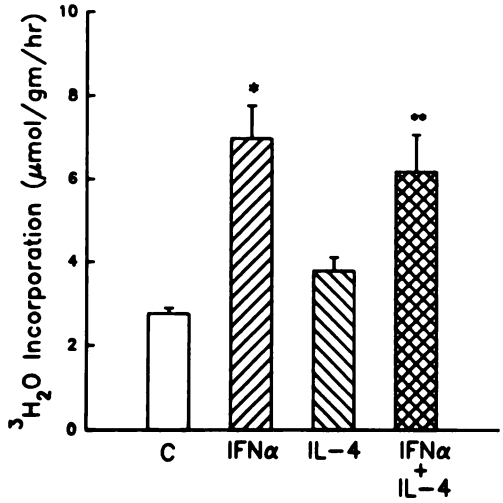


Fig. 6. IL-4 has no effect on IFN-α-stimulated hepatic lipogenesis. Animals were given injections of saline as control, IFN-α (100 μg), IL-4 (100 ng), or a combination of IFN-α (100 μg) and IL-4 (100 ng). Hepatic lipogenesis was measured as in Fig. 1. $n = 5$ for each group. Values are mean ± SE (*bars*). * $P < 0.002$ compared with control. ** $P < 0.02$ compared with control.

and cytokine action has recently been observed (31–38). The data presented here suggest that IL-4 can also inhibit the metabolic effects of certain cytokines.

There are several interesting implications of our studies. (*a*) The specificity of IL-4 inhibition of cytokine-stimulated hepatic lipogenesis confirms our earlier division (26) of lipogenic cytokines into 2 classes that stimulate hepatic lipogenesis by separate mechanisms. IL-4 inhibits class 1 cytokines (TNF, IL-1, and IL-6) but not class 2 cytokines (interferon-$\alpha$). (*b*) It is of interest that IL-4 also blocks the ability of TNF to increase hepatic citrate levels, suggesting that IL-4 blocks an early step in the action of TNF. (*c*) Although the mechanism of IL-4 inhibition is unknown, the inability of IL-4 to suppress basal lipogenesis and the previously discussed specificity suggest that IL-4 works by a mechanism that directly opposes the actions of TNF, IL-1, and IL-6 rather than by a nonspecific effect on hepatic lipid synthesis *per se*. (*d*) The ability of IL-4 to block IL-6 suggests that if IL-6 does mediate TNF- and IL-1-stimulated hepatic lipogenesis, then IL-4 acts distal to the induction of IL-6.

Finally, these data provide evidence for a new activity of cytokines, the ability to inhibit the metabolic effects of other cytokines. The existence of cytokines that can either stimulate hepatic lipogenesis or oppose the ability of other cytokines to stimulate hepatic lipogenesis continues to emphasize the complex interactions between the immune system and lipid metabolism *in vivo*. Thus, the metabolic effect of cytokines resembles their immune functions; cytokines can have overlapping or opposing activities.

Placed in a larger perspective, it is now clear that multiple cytokines acting through multiple receptors influence lipid metabolism at multiple sites by multiple mechanisms (5–7, 9–15, 25–27). These multiple interactions of the immune system provoke the teleological question as to why the immune response is so tightly linked to lipid metabolism. Previous data indicate that the hyperlipidemia induced by cytokines is not necessarily deleterious (45). Daily or twice-daily TNF administration produces prolonged hypertriglyceridemia under conditions in which animals become resistant to the anorectic/cachectic effects of TNF, suggesting that cytokine-induced changes in lipid metabolism are not inevitably linked to wasting (45). Stable hypertriglyceridemia can occur in chronic viral infection, yet there is no link between the hypertriglyceridemia and wasting (46). Given the rapid effects of cytokines on hepatic lipid metabolism, we have previously proposed that these changes represent part of the acute-phase response of the liver (7, 15). It is therefore interesting to speculate as to why cytokines would rapidly increase hepatic lipid synthesis to acutely raise serum triglycerides during an infection. Recent data from our laboratory indicate that VLDL particles can protect animals from the toxicity of endotoxin (47). Earlier studies demonstrated that the binding of endotoxin to high-density lipoprotein decreases the systemic response to endotoxin (48). Lipoproteins can also inactivate viruses (49, 50). Thus, it is possible that the hyperlipidemia of infection is part of the body's host defense mechanisms. It remains to be determined whether the changes in lipid metabolism that occur in cancer have any beneficial effects.

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